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Kimberly J. Prior
(Print Name)

Date: March 30, 2005

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1614

Guido Galley, et al.

Serial No.: 10/767,784

Filed: January 29, 2004

For: **MALONAMIDE DERIVATIVES**

TRANSMITTAL OF CERTIFIED COPY

March 30, 2005

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	03002190.1	February 4, 2003

Respectfully submitted,

Kimberly J. Prior
Attorney for Applicant
Reg. No. 41,483
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153389
KJP/bah
Enclosures

Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03002190.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

CERTIFIED COPY OF
PRIORITY DOCUMENT

Anmeldung Nr:
Application no.: 03002190.1
Demande no:

Anmeldetag:
Date of filing: 04.02.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

4070 Basel
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Malonamide derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D/

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

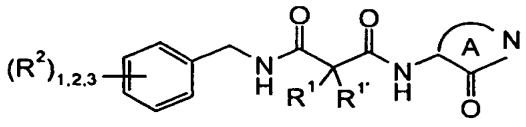
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR LI

F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

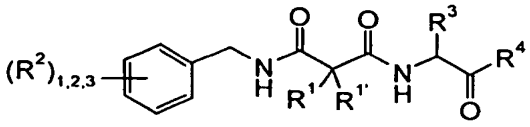
Case 21453

Malonamide derivatives

The invention relates to malonamide derivatives of formula



IA or



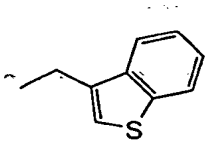
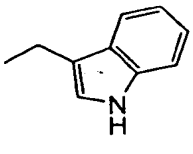
IB

wherein

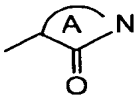
R^1 and $R^{1'}$ are the same or different and are hydrogen, lower alkyl, halogen, benzyl, lower alkenyl or are together with the carbon atom to which they are attached lower cycloalkyl;

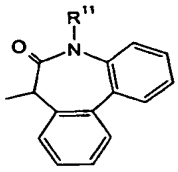
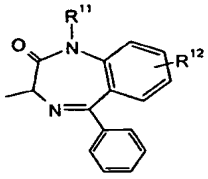
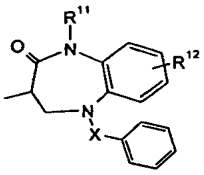
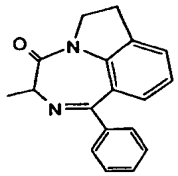
$(R^2)_{1,2,3}$ is independently from each other hydrogen, halogen, lower alkyl, lower alkoxy or trifluoromethyl;

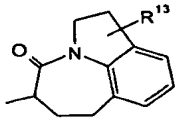
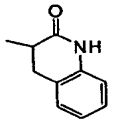
R^3 - is phenyl or benzyl, which are unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or cyano, or is
- lower alkyl,
- two hydrogen atoms,
- $-(CH_2)_{1,2}$-S-lower alkyl,
- $(CH_2)_{1,2}$-cycloalkyl,
- $(CH_2)_{1,2}$-OH,
- CH_2OCH_2-phenyl, or the groups

 or  ;

R^4 is lower alkoxy,
- mono-or dialkyl amino,
- $N(CH_3)(CH_2)_{1,2}$-C≡CH,
or is a mono-, di or tricyclic group, unsubstituted or substituted by R^5 to R^{10}, and which groups may be linked by $-N(CH_3)(CH_2)_{0,1,2}$, to the –C(O) –group in formula IB,

 may be the followings rings

 a),  b),  c)  d)

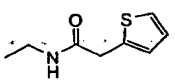
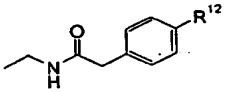
 e) or  f);

wherein

X is $-CH_2$, $-S(O)_2$ or –C(O)-;

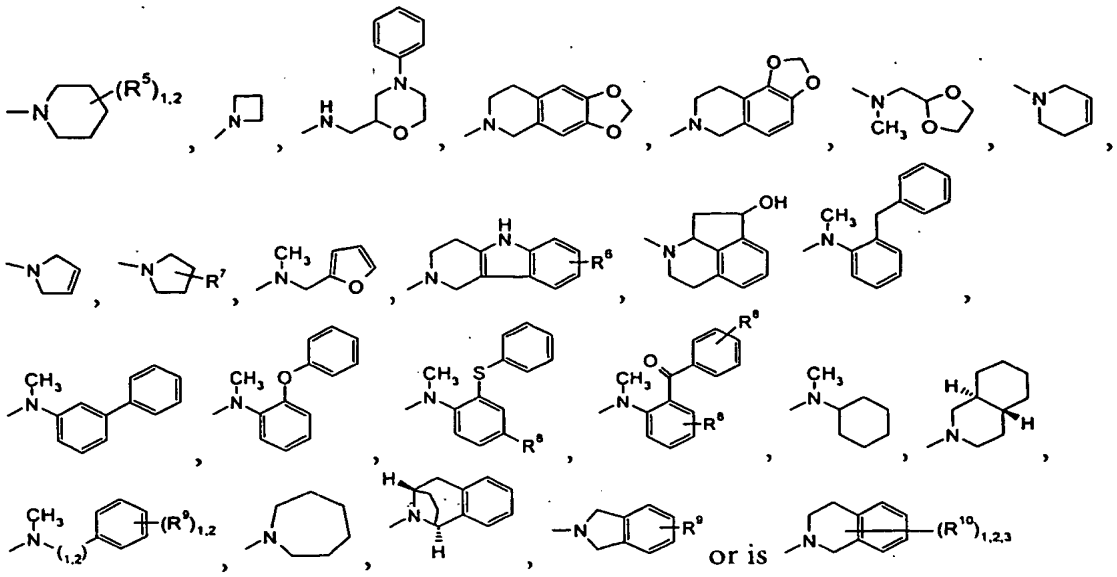
R^{11} is hydrogen or lower alkyl;

R^{12} is hydrogen or halogen;

R^{13} is hydrogen, CN, hydroxy, $-C(O)NH_2$, or  or  ;

and to pharmaceutically suitable acid addition salts thereof.

The mono-, di or tricyclic group, unsubstituted or substituted by R^5 to R^{10}, and which groups may be linked by $-N(CH_3)(CH_2)_{0,1,2,}$ to the –C(O) –group in formula IB, may be the followings:



$(R^5)_{1,2}$ is independently from each other hydrogen, halogen, lower alkyl or $-(CH_2)_{1,2}OH$;

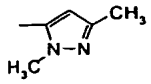
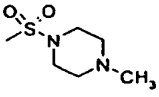
R^6 is hydrogen, halogen or lower alkoxy;

R^7 is hydrogen or $-CH_2OCH_3$;

R^8 is hydrogen or halogen;

R^9 is hydrogen, lower alkoxy, lower alkyl or amino;

$(R^{10})_{1,2,3}$ is independently from each other hydrogen, lower alkyl, lower alkoxy, lower cycloalkyl, halogen, hydroxy, =O, amino, nitro, $-CH_2CN$, $-OCH_2C_6H_5$,

or the groups  ,  ,  ,  or  .

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1 - 4 carbon atoms.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3 – 7 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "lower alkoxy" denotes a group wherein the alkyl residues is as defined above, and which is attached via an oxygen atom.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

It has been found that the compounds of general formulas IA and IB are γ-secretase inhibitors and the related compounds may be useful in the treatment of Alzheimer's disease.

Alzheimer's disease (AD) is the most common cause of dementia in later life. Pathologically AD is characterized by the deposition in the brain of amyloid in extracellular plaques and intracellular neurofibrillary tangles. The amyloid plaques are mainly composed of amyloid peptides (Abeta peptides) which originate from the β-Amyloid Precursor Protein (APP) by a series of proteolytic cleavage steps. Several forms of APP have been identified of which the most abundant are proteins of 695, 751 and 770 amino acids length. They all arise from a single gene through differential splicing. The Abeta peptides are derived from the same domain of the APP but differ at their N- and C-termini, the main species are of 40 and 42 amino-acid length.

Abeta peptides are produced from APP through the sequential action of 2 proteolytic enzymes termed β- and γ-secretase. β-Secretase cleaves first in the extracellular domain of APP just outside of the trans-membrane domain (TM) to produce a C-terminal fragment of APP containing the TM- and cytoplasmatic domain (CTFβ). CTFβ is the substrate for γ-secretase which cleaves at several adjacent positions within the TM to produce the Aβ peptides and the cytoplasmic fragment. The majority of Abeta peptides is of 40 amino acids length (Aβ40), a minor species carries 2 additional amino acids at its C-terminus. Latter is supposed to be the more pathogenic amyloid peptide.

The β-secretase is a typical aspartyl protease. The γ-secretase is a proteolytic activity consisting of several proteins, its exact composition is incompletely understood. However, the presenilins are essential components of this activity and may represent a new group of atypical aspartyl proteases which cleave within the TM of their substates and which are themselves polytopic membrane proteins. Other essential components of γ-secretase may be nicastrin and the products of the aph1 and pen-2 genes. Proven substrates for γ-

secretase are the APP and the proteins of the Notch receptor family, however, γ-secretase has a loose substrate specificity and may cleave further membrane proteins unrelated to APP and Notch.

The γ-secretase activity is absolutely required for the production of Abeta peptides. This has been shown both by genetic means, i.e., ablation of the presenilin genes and by low-molecular-weight inhibitory compounds. Since according to the amyloid hypothesis or AD the production and deposition of Abeta is the ultimate cause for the disease, it is thought that selective and potent inhibitors of γ-secretase will be useful for the prevention and treatment of AD.

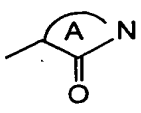
Thus, the compounds of this invention will be useful treating AD by blocking the activity of γ-secretase and reducing or preventing the formation of the various amyloidogenic Abeta peptides.

Numerous documents describe the current knowledge on γ–secretase inhibition, for example the following publications:

Nature Reviews/Neuroscience, Vol. 3, April 2002/281,
Biochemical Society Transactions (2002), Vol. 30. part 4,
Current Topics in Medicinal Chemistry, 2002, 2, 371-383,
Current Medicinal Chemistry, 2002, Vol. 9, No. 11, 1087-1106,
Drug Development Research, 56, 211-227, 2002,
Drug Discovery Today, Vol. 6, No. 9, May 2001, 459-462,
FEBS Letters, 483, (2000), 6-10,
Science, Vol. 297, 353-356, July 2002 and
Journ. of Medicinal Chemistry, Vol. 44, No. 13, 2001, 2039-2060.

Objects of the present invention are the compounds of formula IA or IB per se, the use of compounds of formulas IA or IB and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, related to the γ-secretase inhibition, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formulas IA or IB in the control or prevention of Alzheimer's disease.

A further object of the invention are all forms of optically pure enantiomers, recemates or diastereomeric mixtures for compounds of formulas IA or IB.

The most preferred compounds are those of formula IA, for example for  being a). This are the following specific compounds:

N-(3,5-difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-2-fluoro-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-2-isopropyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-2-ethyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-2-fluoro-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-2,2-dimethyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-propyl-malonamide,

N-benzyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(4-fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(4-chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3-fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

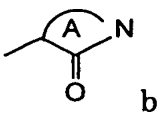
N-(2,5-difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,3,5-trifluoro-benzyl)-malonamide,

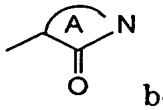
N-(2-fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(2-chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide or

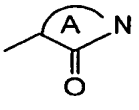
N-(3-chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide.

Further preferred compounds are those of formula IA, for  being b), for example the following compounds:

(N-(3,5-difluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide,
N-(3,5-difluoro-benzyl)-2-fluoro-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide,
N-(3,5-difluoro-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-propyl-malonamide,
N-(3,5-difluoro-benzyl)-2-ethyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide or
N-(4-chloro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide.

Preferred compounds are further those of formula IA, for  being c), for example

N-(5-benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide,
N-(5-benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide or
N-(5-benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide.

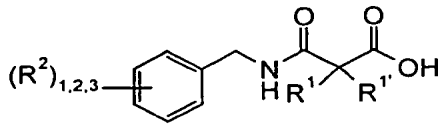
A further preferred group of compounds are those, wherein  is the group e), for example the following compounds:

(2S-cis)-N-(3,5-difluoro-benzyl)-2-methyl-N'-{4-oxo-2-[(2-thiophen-2-yl-acetylamino)-(2R,S)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-malonamide or
(2S-cis)-N-(3,5-difluoro-benzyl)-N'-(2-{[2-(4-fluoro-phenyl)-acetylamino]-methyl}-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-2,2-dimethyl-malonamide.

Furthermore, compounds of formulas IA and IB are preferred, wherein at least one of $(R^2)_{1,2,3}$ is fluoro.

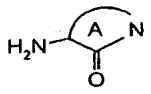
The present compounds of formulas IA and IB and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which processes comprise

a) reacting a compound of formula



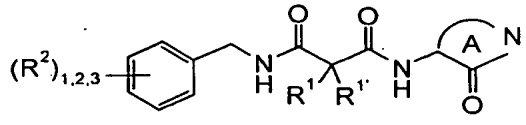
VI

with a compound of formula



VII

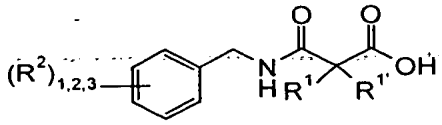
to a compound of formula



IA

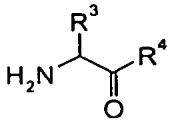
or

b) reacting a compound of formula



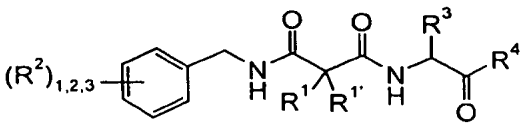
VI

with a compound of formula



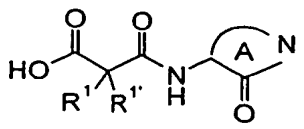
VIII

to a compound of formula



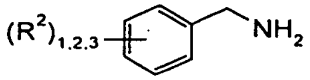
IB

c) reacting a compound of formula



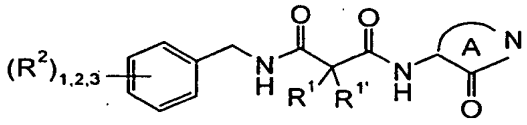
X

with a compound of formula

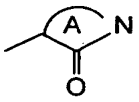


IV

to a compound of formula



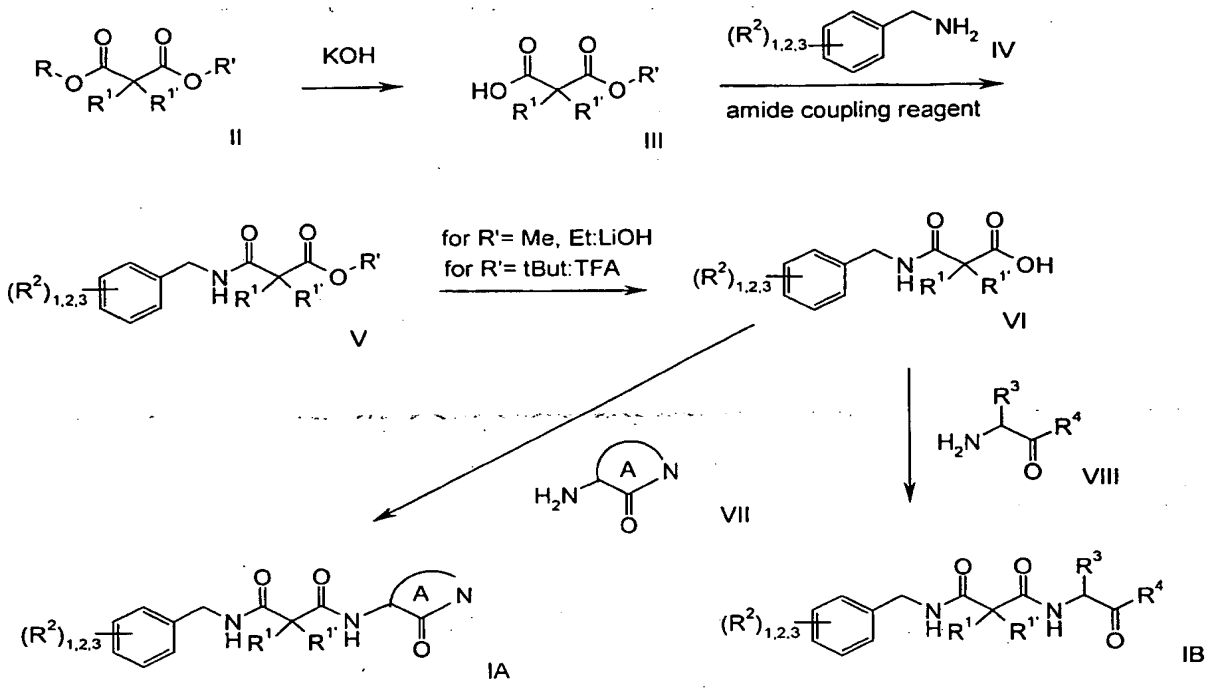
IA

wherein the substituents R^1, $R^{1'}$, R^2 and the group  are described above, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formulas IA and IB may be prepared in accordance with the following schemes 1, 2, and 3:

Scheme 1



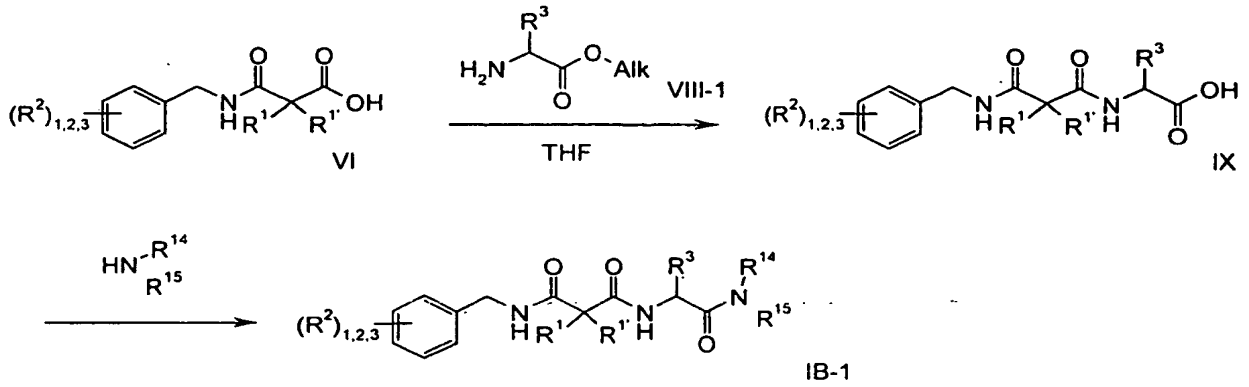
In this scheme R and R' are independently from each other lower alkyl and R^1, $R^{1'}$, R^2, R^3 and R^4 are as described above.

The detailed description can be found below and in Examples 1 – 152, 161.

To a solution of potassium or sodium hydroxide in a solvent, such as ethanol, a methyl-malonate of formula II is added and the mixture is refluxed for about 4 hours. After cooling the reaction mixture is concentrated and dried in conventinal manner and used without further purification in the next step. To a solution of the obtained methyl-malonic acid monoethyl ester (III) in tetrahydrofuran, a compound of formula IV, for example 3,5-difluorobenzylamine, of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, of 1-hydroxybenzotrizole hydrate and of N,N-diisopropyl-ethylamine are added. The mixture is stirred at room temperature for about 18 h. After concentration in vacuo HCl is added and the mixture is extracted, dried and purified as usual. To the obtained solution of a compound of formula V water and lithium hydroxide are added and the mixture is refluxed for about 5 hours. After purification a compound of formula IA may be obtained as follows: To a solution of a compound of formula VI, for example N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid in tetrahydrofuran, a compound of formula VII, of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, of 1-hydroxybenzotrizole hydrate and of N,N-diisopropyl-ethylamine are added. The mixture is stirred at room temperature for about 18 h. After concentrating, drying and purifying a

compound of formula IA is obtained. A compound of formula IB may be obtained under the same conditions as described above, using a compound of formula VIII.

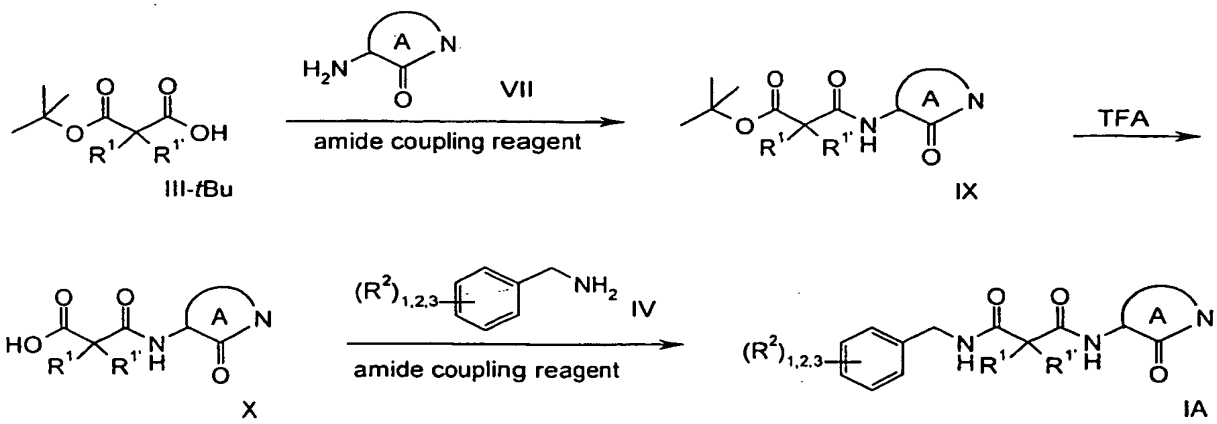
Scheme 2



The compounds of formula IB-1 may be prepared as described in scheme 1 for the last step (VI with VII or VIII→IA or IB).

The compounds of formula IB-1 are identical with those of formula IB, wherein R^1, $R^{1'}$, R^2 and R^3 are described as above and wherein R^4 is $-NR^{14}R^{15}$,
R^{14} is hydrogen or lower alkyl and
R^{15} is lower alkyl, $-(CH_2)_{1,2}-C\equiv CH$ or $-(CH_2)_{0,1,2}$-mono-, di or tricyclic group, unsubstituted or substituted by R^5 to R^{10} as described above.

Scheme 3



In this scheme R and R' are independently from each other lower alkyl and the other groups are as described above.

The detailed description can be found below and in Examples 153 – 160.

To a solution of the obtained methyl-malonic acid mono-tert-butyl ester (III-tBu) in tetrahydrofuran, a compound of formula VII, for example 7-Amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 1-hydroxybenzotrizole and N,N-diisopropyl-ethylamine are added. The mixture is stirred at room temperature for about 12 h. After purification, a compound of formula IX was obtained which was treated with an acid, for instance TFA, in a suitable solvent, for instance dichloromethane, to give a compound of formula X. Using compounds of formula X and VII, compounds of formula IA can be obtained following the amide coupling procedure described above.

Some compounds of formula IA or IB may be converted to a corresponding acid addition salt, for example compounds, containing an amine group.

The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids suchas acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of compounds of formula IA or IB may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formulas IA and IB and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention may inhibit the γ-secretase.

The compounds were investigated in accordance with the test given hereinafter.

Description of γ-secretase assay

The activity of test compounds can be evaluated in assays which measure the proteolytic cleavage of suitable substrates by γ-secretase activity. These can be cellular assays where e.g., a substrate of the γ-secretase is fused in its cytoplasmic domain to a transcription factor. Cells are transfected with this fusion gene and a reporter gene, e.g.,

firefly luciferase, which expression is enhanced by the transcription factor. Cleavage of the fused substrate by γ-secretase will lead to expression of the reporter gene which can be monitored in appropriate assays. The γ-secretase activity can also be determined in cell-free in vitro asays where e.g., a cell lysate containing the γ-secretase complex is incubated with a suitable APP-derived substrate which is cleaved to the Abeta peptides. The amount of produced peptides can be determined with specific ELISA assays. Cell lines of neuronal origin secrete Abeta peptides which can be measured with the specific ELISA assay. Treatment with compounds which inhibit γ-secretase leads to a reduction of secreted Abeta thus providing a measure of inhibition.

The in vitro assay of γ-secretase activity uses a HEK293 membrane fraction as a source of γ-secretase and a recombinant APP substrate. Latter consist of the C-terminal 100 amino acids of human APP fused to a 6xHistidin tail for purification which is expressed in E.coli in a regulatable expression vector, e.g. pEt15. This recombinant protein corresponds to the truncated APP fragment which results after β-secretase cleavage of the extracellular domain and which constitutes the γ-secretase substrate. The assay principle is described in Li YM et al, PNAS 97(11), 6138-6143 (2000). Hek293 cells are mechanically disrupted and the microsomal fraction is isolated by differential centrifugation. The membranes are solubilized in detergent (0.25 % CHAPSO) and incubated with the APP substrate. The Abeta peptides which are produced by γ-secretase cleavage of the substrate are detected by specific ELISA assays as described (Brockhaus M et al, Neuroreport 9(7), 1481-1486 (1998).

The preferred compounds show a IC_{50}<1.0. In the list below are described some data to the γ-secretase inhibition:

Example No.	IC_{50} in vitro	Example No.	IC_{50} in vitro
1	0.083	118	0.041
2	0.021	119	0.019
13	0.05	125	0.015
14	0.018	127	0.064
15	0.004	130	0.052

17	0.25	132	0.043
22	0.70	135	0.04
103	0.92	136	0.03
104	0.72	143	0.1
108	0.027	153	0.09
111	0.04	154	0.08
114	0.003	159	0.09
115	0.087	164	0.1
116	0.008	167	0.045
117	0.011		

The compounds of formula IA or IB and the pharmaceutically acceptable salts of the compounds of formula IA or IB can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula IA or IB can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying

the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula IA and IB or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula IA and IB and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula IA and IB as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the inhibition of the γ-secretase, such as of Alzheimer's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula IA or IB	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water..
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula IA or IB	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 1

(N-(3,5-Difluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

a) 2-Methyl-malonic acid monoethyl ester

To a solution of 6.44 g (115 mmol) potassium hydroxide in 200 ml of ethanol 20.0 g diethyl methyl-malonate (115 mmol) was added and the mixture was refluxed for 4 hours. After cooling the reaction mixture was concentrated on a rotary evaporator, 50 ml of water was added and the mixture was extracted with ether (two times 50 ml). The aqueous solution was acidified with 4M hydrochloric acid and extracted with ethyl acetate (three times 50 ml). The combined organic layers were dried (MgSO4), concentrated under reduced pressure and used without further purification.

MS m/e (%): 101.1 (M-EtO, 100), 147.1 ($M+H^+$, 8).

b) N-(3,5-Difluoro-benzyl)-2-methyl-malonamic acid ethyl ester

To a solution of 2.92 g (20 mmol) methyl-malonic acid monoethyl ester in 100 ml of tetrahydrofuran 2.86 g (20 mmol) of 3,5-difluorobenzylamine, 3.83 g (20 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 2.70 g (20 mmol) of 1-hydroxybenzotrizole hydrate and 2.58 g (20 mmol) of N,N-diisopropyl-ethylamine were added. The mixture was stirred at room temperature for 18 h. After concentration in vacuo 0.5 N HCl (50 ml) was added and the mixture was extracted with dichloromethane (three times 50 ml). The combined organic layers were extracted with 0.5 N aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate = 3:1) to yield 4.29 g (79 %) of the title compound as white crystalline solid.

MS m/e (%): 272.2 ($M+H^+$, 100).

c) N-(3,5-Difluoro-benzyl)-2-methyl-malonamic acid

To a solution of 4.0 g (14.75 mmol) N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid ethyl ester in 300 ml of ethanol, 15 ml of water and 1.41 g (59 mmol) of lithium hydroxide were added and the mixture was refluxed for 5 hours. After concentration in vacuo water (50 ml) was added and the mixture was extracted with dichloromethane (three times 30 ml). The aqueous phase was acidified with 8 N hydrochloric acid and extracted with dichloromethane (four times 30 ml).

The combined organic layers from the second extraction were dried ($MgSO_4$) and evaporated in vacuo to yield an orange oil. The mixture was dissolved in a small amount of

ethyl acetate and hexane and left overnight. The resulting white crystals were collected by filtration to give 11.4 g (74.8 %) of the title compound.
MS m/e (%): 142.1 ($C_6H_3F_2$-CH=NH_2^+, 100), 243.1 ($M+H^+$, 16).

d) (RS..)-N-(3,5-Difluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

To a solution of 0.073 g (0.3 mmol) N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid in 5 ml of tetrahydrofuran 0.080 g (0.3 mmol) of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, 0.058 g (0.3 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 0.040 g (0.3 mmol) of 1-hydroxybenzotrizole hydrate and 0.039 g (0.3 mmol) of N,N-diisopropyl-ethylamine were added. The mixture was stirred at room temperature for 18 h. After concentration in vacuo 0.5 N HCl (5 ml) was added and the mixture was extracted with dichloromethane (three times 5 ml). The combined organic layers were extracted with 0.5 N aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate = 3:1) to yield 0.099 g (67 %) of the diastereomeric mixture of title compound as white solid.
MS m/e (%):491.2 ($M+H^+$, 100).

Example 2

N-(3,5-Difluoro-benzyl)-2-fluoro-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using 2-fluoro-2-methyl-malonic acid diethyl ester instead of diethyl methyl-malonate in step a).
MS m/e (%): 509.3 ($M+H^+$, 100).

Example 3

(3RS)-N-(3,5-Difluoro-benzyl)-2,2-dimethyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using 2,2-dimethyl-malonic acid diethyl ester instead of diethyl methyl-malonate in step a).
MS m/e (%): 505.2 ($M+H^+$, 100).

Example 4

(3RS)-N-(3,5-Difluoro-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using diethyl malonate instead of diethyl methyl-malonate in step a).

MS m/e (%): 477.2 ($M+H^+$, 100).

Example 5

N-(3,5-Difluoro-benzyl)-2-fluoro-2-methyl-N'-(4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]diazepino[6,7,1-hi]indol-3-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using 2-fluoro-2-methyl-malonic acid diethyl ester instead of diethyl methyl-malonate in step a) and (3RS)-3-amino-1-phenyl-6,7-dihydro-3H-[1,4]diazepino[6,7,1-hi]indol-4-one instead of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).

MS m/e (%): 521.1 ($M+H^+$, 100).

Example 6

N-(3,5-Difluoro-benzyl)-2-methyl-N'-{(S)-phenyl-[(4-phenyl-morpholin-2-ylmethyl)-carbamoyl]-methyl}-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using (2S)-2-amino-2-phenyl-N-((2RS)-4-phenyl-morpholin-2-ylmethyl)-acetamide instead of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).

MS m/e (%): 551.2 ($M+H^+$, 100).

Example 7

(2S)-2-[2-(RS)-(3,5-Difluoro-benzylcarbamoyl)-propionylamino]-phenyl-acetic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures described for example 1 using (S)-phenylglycine tert.butyl ester instead of (3RS)-3-amino-

1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).
MS m/e (%): 377.3 ($M+H^+$, 100).

Example 8

(3RS)-Cyclopropane-1,1-dicarboxylic acid 3,5-difluoro-benzylamide (1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide
The title compound was obtained in comparable yields according to the procedures described for example 1 using cyclopropane-1,1-dicarboxylic acid diethyl ester instead of diethyl methyl-malonate in step a).
MS m/e (%): 503.3 ($M+H^+$, 100).

Example 9

(2RS)-N-[(1S)-1-(Cyclohexyl-methyl-carbamoyl)-1-phenyl-methyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide
The title compound was obtained in comparable yields according to the procedures described for example 1 using (2S)-2-amino-N-cyclohexyl-N-methyl-2-phenyl-acetamide instead of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).
MS m/e (%): 472.3 ($M+H^+$, 100).

Example 10

(2S)-2-[(2RS)-2-(3,5-Difluoro-benzylcarbamoyl)-propionylamino]-3-phenyl-propionic acid tert-butyl ester
The title compound was obtained in comparable yields according to the procedures described for example 1 using (S)-phenylalanine tert.butyl ester instead of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).
MS m/e (%): 391.2 ($M+H^+$, 100).

Example 11

(2S)-2-[(2RS)-2-(3,5-Difluoro-benzylcarbamoyl)-2-fluoro-propionylamino]-2-phenyl-acetic acid tert-butyl ester
The title compound was obtained in comparable yields according to the procedures described for example 1 using 2-fluoro-2-methyl-malonic acid diethyl ester instead of diethyl methyl-malonate in step a) and (S)-phenylglycine tert.butyl ester instead of (3RS)-

3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).
MS m/e (%): 473.1 ($M+Na^+$, 100), 451.0 ($M+H^+$, 29).

Example 12

N-(3,5-Difluoro-benzyl)-2-fluoro-2-methyl-N'-(2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl)-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using 2-fluoro-2-methyl-malonic acid diethyl ester instead of diethyl methyl-malonate in step a) and (RS)-3-amino-3,4-dihydro-1H-quinolin-2-one instead of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).
MS m/e (%): 406.4 ($M+H^+$, 100).

Example 13

N-(5-Benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

a) (1-Methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester

To a solution of 0.94 g (3.38 mmol) (S)-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester dissolved in 20 ml of tetrahydrofurane at –78°C , 3.4 ml of lithium bis(trimethylsilyl)amide (1N solution in tetrahydrofurane) were added. The reaction mixture was stirred for 30 minutes at – 78 °C and was allowed to reach room temperature. Iodomethane was slowly added and stirring was continued for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHSO_4$ solution and separated. The aqueous phase was extracted twice with ethyl acetate (2 x 50 ml). The combined organic layers were washed with water (2 x 100 ml), with brine (1x 100 ml), dried over $MgSO_4$, filtered and evaporated. The residue was purified by chromatography (heptane/ethyl acetate = 7:3) to yield 0.855 g (87 %) of the product as a light yellow solid.
MS m/e (%): 292.2 ($M+H^+$, 100)

b) (5-Benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl

To a solution of 0.087 g (1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in 1 ml of dimethylformamide 0.138 g of potassium carbonate and 0.062 g of benzyl bromide were added. The reaction mixture was shaken for

16 hours at room temperature. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over MgSO4, filtered and evaporated. The residue was purified by chromatography (heptane/ethyl acetate = 2:1) to yield 0.10 g (87 %) of the product as a light yellow foam.
MS m/e (%): 382.3 ($M+H^+$, 100).

c) N-(5-Benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

To a solution of 0.086 g (5-benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in 1 ml of dichloromethane, 1 ml of trifluoracetic acid was added. The reaction mixture was allowed to stir at room temperature for 2-3 h while monitoring the reaction progress by LC-MS. Upon completion of the reaction, the solvent and excess of trifluoracetic acid were evaporated and the residue was dried under high vacuo for 1 hour. To the foam obtained dissolved in 1 ml of tetrahydrofurane, 0.060 g N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid 0.043 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 0.030 g of 1-hydroxybenzotrizole hydrate and 0.087 g of N,N-diisopropyl-ethylamine were added. After stirring the mixture at room temperature for 18 h, 0.5 N HCl (1 ml) was added and the mixture was extracted with dichloromethane (2 ml) The organic layer was extracted with 0.5 N aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated on the rotary evaporator. The residue was crystallized with heptane/EtOAc=4:1 to yield 0.057 g (50 %) of the epimeric mixture of title compound as white solid.
MS m/e (%): 507.3 ($M+H^+$, 100).

Example 14

N-(5-Benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

a) (5-Benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester

To a solution of 0.087 g (1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in 1 ml of dichloromethane, 0.064 g of benzene sulfonyl chloride and 0.052 g of pyridine were added. The reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched by addition of 1 M HCl (1 ml) and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated on the rotary evaporator to yield 0.113 g (95 %) of the

product as a light yellow foam.
MS m/e (%): 432.3 ($M+H^+$, 100).

b) N-(5-Benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound was obtained in comparable yields according to the procedure described for example 13c) using (5-benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester instead of (5-benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester.
MS m/e (%): 557.2 ($M+H^+$, 100).

Example 15

N-(5-Benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

a) (5-Benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester

To a solution of 0.087 g (1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester in 1 ml of dichloromethane, 0.051 g of benzoyl chloride and 0.061 g of triethylamine were added. The reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched by addition of 1 M HCl (1 ml) and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated on the rotary evaporator to yield 0.125 g (97 %) of the product as a light yellow foam.
MS m/e (%): 396.3 ($M+H^+$, 100).

b) N-(5-Benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound was obtained in comparable yields according to the procedure described for example 13c) using (5-benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester instead of (5-benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-carbamic acid tert-butyl ester.
MS m/e (%): 521.3 ($M+H^+$, 100).

Example 16

N-(7-Chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 1 using (3RS)-3-amino-1,3-dihydro-7-chloro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one instead of (3RS)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in step d).

MS m/e (%): 525.3 ($M+H^+$, 100).

Example 17

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

a)[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

tert-Butyloxycarbonyl-L-tryptophan (3.00g, 9.9mmol) and 1,2,3,4-Tetrahydroisoquinoline (1.31g, 9.9mmol) were suspended in THF (20ml). At a temperature of 0 °C, hydroxybenzotriazole (1.33g, 9.9mmol), diisopropylethylamine (1.27g, 9.9mmol), and EDC (N-3-dimethylaminopropyl-N'-ethylcarbodiimide hydrochloride, 1.89g, 9.9mmol) were added. The reaction mixture was stirred overnight at r.t. The solvent was evaporated, the residue was taken up in ethyl acetate, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 420.5 ($M+H^+$), (2.90g, 70 %) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

b) 2-Amino-1-(3,4-dihydro-1H-isoquinolin-2-yl)-3-(1H-indol-3-yl)-propan-1-one

[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (2.90g, 6.91mmol) was dissolved in CH_2Cl_2 (10ml). Trifluoroacetic acid (10ml) was added and the mixture was stirred for 90 minutes at r.t. until analytical HPLC indicated complete consumption of the starting material. The solvent was evaporated , the residue was taken up in ethyl acetate, washed (water), and dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 320.4 ($M+H^+$), (1.73 g, 69 %) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

c) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

2-Amino-1-(3,4-dihydro-1H-isoquinolin-2-yl)-3-(1H-indol-3-yl)-propan-1-one (57 mg, 0.18 mmol) was placed in a disposable polypropylene tube and dissolved in DMF (1ml). TBTU (O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium-tetrafluoroborate, 65 mg, 0.2 mmol) and N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (49mg, 0.2mmol) were added, and the mixture was shaken overnight at r.t. The title compound, MS: m/e = 545.3 ($M+H^+$), was isolated from the reaction mixture by automated, preparative HPLC (YMC CombiPrep C18 column 50 x 20 mm, solvent gradient 5-95 % CH_3CN in 0.1 % TFA(aq) over 6.0 min, λ = 230 nm, flow rate 40 ml/min).

Example 18

N-[1-Benzyl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 506.3 ($M+H^+$), was prepared in analogy to example 17 from tert-butyloxycarbonyl-L-phenylalanine.

Example 19

N-[1-Benzyloxymethyl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 536.4 ($M+H^+$), was prepared in analogy to example 17 from N-(*tert*-butoxycarbonyl)-O-benzyl-L-serine.

Example 20

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-1-(*S*)phenyl-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 492.3 ($M+H^+$), was prepared in analogy to example 17 from N-alpha-(*tert*-butoxycarbonyl)-L-phenylglycine.

Example 21

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-1-(*R*)-phenyl-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 492.3 ($M+H^+$), was prepared in analogy to example 17 from N-alpha-(*tert*-butoxycarbonyl)-D-phenylglycine.

Example 22

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-hydroxymethyl-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 446.3 ($M+H^+$), was prepared in analogy to example 17 from *tert*-butyloxycarbonyl-L-serine.

Example 23

N-[1-(4-Chloro-benzyl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 540.4 (M^+), was prepared in analogy to example 17 from N-alpha-(*tert*-butyloxycarbonyl)-*p*-chloro-L-phenylalanine.

Example 24

N-[1-Benzo[b]thiophen-3-ylmethyl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 562.4 ($M+H^+$), was prepared in analogy to example 17 from N-alpha-(*tert*-butyloxycarbonyl)-L-benzothienylalanine.

Example 25

N-[1-(3,4-Dichloro-benzyl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 574.3 (M^+), was prepared in analogy to example 17 from N-alpha-(*tert*-butyloxycarbonyl)-*m*, *p*-dichloro-L-phenylalanine.

Example 26

N-[1-Cyclohexylmethyl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 511.6 ($M+H^+$), was prepared in analogy to example 17 from N-alpha-(*tert*-butyloxycarbonyl)- L-cyclohexylalanine.

Example 27

N-(3,5-Difluoro-benzyl)-N'-[1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-3-methylsulfanyl-propyl]-2-methyl-malonamide

The title compound, MS: m/e = 490.4 ($M+H^+$), was prepared in analogy to example 17 from *tert*-butyloxycarbonyl-L-methionine.

Example 28

N-(3,5-Difluoro-benzyl)-N'-[1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-pentyl]-2-methyl-malonamide

The title compound, MS: m/e = 472.3 ($M+H^+$), was prepared in analogy to example 17 from N-alpha-*tert*-butyloxycarbonyl-L-2-aminocaproic acid.

Example 29

N-(3,5-Difluoro-benzyl)-N'-[1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-3,3-dimethyl-butyl]-2-methyl-malonamide

The title compound, MS: m/e = 486.4 ($M+H^+$), was prepared in analogy to example 17 from *tert*-butyloxycarbonyl-L-neopentylglycine.

Example 30

N-(3,5-Difluoro-benzyl)-N'-[1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-propyl]-2-methyl-malonamide

The title compound, MS: m/e = 444.4 ($M+H^+$), was prepared in analogy to example 17 from *tert*-butyloxycarbonyl-L-2-aminobutanoic acid.

Example 31

N-[1-(2-Cyano-benzyl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 531.4 ($M+H^+$), was prepared in analogy to example 17 from N-alpha-(*tert*-butyloxycarbonyl)-*o*-cyano-L-phenylalanine.

Example 32

N-(3,5-Difluoro-benzyl)-N'-[1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-2-methyl-butyl]-2-methyl-malonamide

The title compound, MS: m/e = 472.4 ($M+H^+$), was prepared in analogy to example 17 from *tert*-butyloxycarbonyl-L-isoleucine.

Example 33

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-2-methyl-malonamide

a) 2-[2-(3,5-Difluoro-benzylcarbamoyl)-propionylamino]-3-(1H-indol-3-yl)-propionic acid tert-butyl ester

N-(3,5-Difluoro-benzyl)-2-methyl-malonamic acid (3.00 g, 12.3 mmol), L-tryptophan-*tert*-butylester hydrochloride (3.66 g, 12.3 mmol), TBTU (O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium-tetrafluoroborate, 3.96 g, 12.3 mmol) and triethylamin (3.74 g, 3.70 mmol) were dissolved in DMF (15 ml) and stirred for 5 h at r.t.. The reaction mixture was poured into water and the product mixture was extracted with ethyl acetate. The organic layers were dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 486.4 ($M+H^+$), (6.45 g, quant.) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

b) 2-[2-(3,5-Difluoro-benzylcarbamoyl)-propionylamino]-3-(1H-indol-3-yl)-propionic acid

2-[2-(3,5-Difluoro-benzylcarbamoyl)-propionylamino]-3-(1H-indol-3-yl)-propionic acid *tert*-butyl ester (5.99 g, 12.3 mmol) was dissolved in dichloromethane (15 ml), and trifluoroacetic acid (15 ml) was added at 0 °C. The mixture was stirred overnight at r.t. until all starting material was consumed (analytical HPLC). The volatiles were evaporated, the residue was taken up in ethyl acetate and washed with water. The organic layers were dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 429.4 ($M+H^+$), (3.5 g, 66 %) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

c) N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-2-methyl-malonamide

2-[2-(3,5-Difluoro-benzylcarbamoyl)-propionylamino]-3-(1H-indol-3-yl)-propionic acid (64 mg, 0.15 mmol) was placed in a disposable polypropylene tube and dissolved in DMF (1ml). TPTU (O-[2-oxo-1(2H)-pyridyl]-N, N, N', N'-tetramethyluronium-tetrafluoroborate, 49 mg, 0.165 mmol) and 6-methoxy-1,2,3,4-tetrahydro-isoquinoline (24 mg, 0.15 mmol) were added, and the mixture was shaken overnight at r.t. The title compound, MS: m/e = 575.3 ($M+H^+$), was isolated from the reaction mixture by automated, preparative HPLC (YMC CombiPrep C18 column 50 x 20 mm, solvent gradient 5-95 % CH_3CN in 0.1 % TFA(aq) over 6.0 min, λ = 230 nm, flow rate 40 ml/min).

Example 34

N-{1-Benzyl-2-[1-(2,5-dimethyl-2H-pyrazol-3-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-2-oxo-ethyl}-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 600.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and (RS)-1-(2,5-Dimethyl-2H-pyrazol-3-yl)-1,2,3,4-tetrahydro-isoquinoline.

Example 35

N-[1-Benzyl-2-(5-benzyloxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 612.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 5-benzyloxy-1,2,3,4-tetrahydro-isoquinoline.

Example 36

N-[2-(8-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 579.3 ($M+H^+$), was prepared in analogy to example 33 from 8-chloro-1,2,3,4-tetrahydro-isoquinoline.

Example 37

N-[1-Benzyl-2-(6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 536.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 6-methoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 38

N-(3,5-Difluoro-benzyl)-N'-[2-(7,8-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 605.3 ($M+H^+$), was prepared in analogy to example 33 from 7,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 39

N-[1-Benzyl-2-oxo-2-(1-pyrazin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 584.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and (RS)-1-pyrazin-2-yl-1,2,3,4-tetrahydro-isoquinoline.

Example 40

N-[1-Benzyl-2-(4-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 520.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 4-methyl-1,2,3,4-tetrahydro-isoquinoline.

Example 41

N-(3,5-Difluoro-benzyl)-N'-[2-(1,3-dihydro-isoindol-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 531.3 ($M+H^+$), was prepared in analogy to example 33 from isoindoline.

Example 42

N-(3,5-Difluoro-benzyl)-N'-[2-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isoquinolin-8-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 589.5 ($M+H^+$), was prepared in analogy to example 33 from 6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinoline.

Example 43

N-[1-Benzyl-2-oxo-2-(1-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 583.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 1,2,3,4-tetrahydro-1-(2-pyridyl)isoquinoline.

Example 44

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(4-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 559.4 ($M+H^+$), was prepared in analogy to example 33 from 4-methyl-1,2,3,4-tetrahydro-isoquinoline.

Example 45

N-[2-(9-Aza-tricyclo[6.2.2.0 2,7]dodeca-2,4,6-trien-9-yl)-1-benzyl-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 532.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 9-aza-tricyclo[6.2.2.0 2,7]dodeca-2,4,6-triene.

Example 46

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-oxo-2-(6,7,8-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 635.4 ($M+H^+$), was prepared in analogy to example 33 from 6,7,8-trimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 47

N-{1-Benzyl-2-[7-(4-methyl-piperazine-1-sulfonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2-oxo-ethyl}-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 668.5 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 7-(4-methyl-piperazine-1-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline.

Example 48

N-[1-Benzyl-2-oxo-2-(1,3,4,9-tetrahydro-b-carbolin-2-yl)-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 545.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 1,2,3,4-tetrahydro-beta-carboline.

Example 49

N-[1-Benzyl-2-(5-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 540.4 (M^+), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 5-chloro-1,2,3,4-tetrahydro-isoquinoline.

Example 50

N-(3,5-Difluoro-benzyl)-N'-[2-(4,4-difluoro-piperidin-1-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 533.4 ($M+H^+$), was prepared in analogy to example 33 from 4,4-difluoropiperidine.

Example 51

N-[1-Benzyl-2-(7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 550.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 5,6,7,8-tetrahydro-1,3-dioxolo(4,5-G)isoquinoline.

Example 52

N-[1-Benzyl-2-oxo-2-(1-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 584.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 1-pyrimidin-5-yl-1,2,3,4-tetrahydro-isoquinoline.

Example 53

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(3-methyl-piperidin-1-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 511.4 ($M+H^+$), was prepared in analogy to example 33 from 3-methylpiperidine.

Example 54

N-[1-Benzyl-2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 566.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 55

N-[1-Benzyl-2-(octahydro-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 512.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and *trans*-decahydroisoquinoline.

Example 56

N-[1-Benzyl-2-(1,3-dihydro-isoindol-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 492.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and Isoindoline.

Example 57

N-(3,5-Difluoro-benzyl)-N'-[2-(3,6-dihydro-2H-pyridin-1-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 494.6 ($M+H^+$), was prepared in analogy to example 33 from 1,2,3,6-tetrahydropyridine.

Example 58

N-[1-Benzyl-2-(6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isoquinolin-8-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 550.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinoline.

Example 59

N-[1-Benzyl-2-oxo-2-(6,7,8-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 596.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 6,7,8-trimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 60

N-(1-Benzyl-2-oxo-2-piperidin-1-yl-ethyl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 458.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and piperidine.

Example 61

N-(3,5-Difluoro-benzyl)-N'-[2-(4-fluoro-piperidin-1-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 515.4 ($M+H^+$), was prepared in analogy to example 33 from 4-fluoropiperidine.

Example 62

N-(3,5-Difluoro-benzyl)-N'-[2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 605.3 ($M+H^+$), was prepared in analogy to example 33 from 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 63

N-(3,5-Difluoro-benzyl)-N'-[2-(2,5-dihydro-pyrrol-1-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 481.4($M+H^+$), was prepared in analogy to example 33 from1-isopropyl-1,2,3,4-tetrahydro-isoquinoline.

Example 64

N-[1-Benzyl-2-(1-isopropyl-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 548.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and isopropyl-1,2,3,4-tetrahydro-isoquinoline.

Example 65

N-[1-Benzyl-2-(3,6-dihydro-2H-pyridin-1-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 456.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 8-chloro-1,2,3,4-tetrahydro-isoquinoline.

Example 66

N-[1-Benzyl-2-(8-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 540.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 8-chloro-1,2,3,4-tetrahydro-isoquinoline.

Example 67

N-[1-Benzyl-2-(1-cyanomethyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 605.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 1-cyanomethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 68

N-[1-Benzyl-2-(7-bromo-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 586.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 7-bromo-1,2,3,4-tetrahydro-isoquinoline.

Example 69

N-[2-(6,7-Diethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 633.4 ($M+H^+$), was prepared in analogy to example 33 from 6,7-diethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 70

N-[2-(4-Amino-1,3-dihydro-isoindol-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 546.4 ($M+H^+$), was prepared in analogy to example 33 from 2,3-dihydro-1H-isoindol-4-ylamine.

Example 71

N-[2-(5-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 579.3 (M^+), was prepared in analogy to example 33 from 8-chloro-1,2,3,4-tetrahydro-isoquinoline.

Example 72

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-oxo-2-pyrrolidin-1-yl-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 483.3 ($M+H^+$), was prepared in analogy to example 33 from pyrrolidine.

Example 73

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(2-methoxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 527.3 ($M+H^+$), was prepared in analogy to example 33 from 2-methoxymethyl-pyrrolidin.

Example 74

N-[2-(7,8-Dichloro-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 613.3 ($M+H^+$), was prepared in analogy to example 33 from 7,8-dichloro-1,2,3,4-tetrahydro-isoquinoline.

Example 75

N-[1-(Benzyl-methyl-carbamoyl)-2-phenyl-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 494.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and benzyl-methyl-amine.

Example 76

N-[2-Azepan-1-yl-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 511.4 ($M+H^+$), was prepared in analogy to example 33 from azepane.

Example 77

N-(3,5-Difluoro-benzyl)-N'-[1-dimethylcarbamoyl-2-(1H-indol-3-yl)-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 457.5 ($M+H^+$), was prepared in analogy to example 33 from dimethylamine.

Example 78

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 590.4 ($M+H^+$), was prepared in analogy to example 33 from 7-nitro-1,2,3,4-tetrahydro-isoquinoline.

Example 79

N-[1-Benzyl-2-(1-cyclopropyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 606.5 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 1-cyclopropyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 80

N-[2-(7-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 579.3 ($M+H^+$), was prepared in analogy to example 33 from 7-chloro-1,2,3,4-tetrahydro-isoquinoline.

Example 81

N-(1-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 444.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and pyrrolidine.

Example 82

N-[1-Benzyl-2-(7,8-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 566.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 7,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

Example 83

N-(3,5-Difluoro-benzyl)-N'-[1-(furan-2-ylmethyl-methyl-carbamoyl)-2-(1H-indol-3-yl)-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 523.3 ($M+H^+$), was prepared in analogy to example 33 from furan-2-ylmethyl-methyl-amine.

Example 84

N-[2-(7-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 625.3 ($M+H^+$), was prepared in analogy to example 33 from 7-bromo-1,2,3,4-tetrahydro-isoquinoline.

Example 85

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 559.4 ($M+H^+$), was prepared in analogy to example 33 from 1-methyl-1,2,3,4-tetrahydro-isoquinoline.

Example 86

N-(3,5-Difluoro-benzyl)-N'-[2-(1-hydroxy-2,2a,4,5-tetrahydro-1H-3-aza-acenaphthylen-3-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 587.4 ($M+H^+$), was prepared in analogy to example 33 from 1,2,2a,3,4,5-hexahydro-3-aza-acenaphthylen-1-ol.

Example 87

N-(3,5-Difluoro-benzyl)-2-methyl-N'-[1-(methyl-prop-2-ynyl-carbamoyl)-2-phenyl-ethyl]-malonamide

The title compound, MS: m/e = 442.3 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and methylpropargylamine.

Example 88

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(2-methoxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 527.4 ($M+H^+$), was prepared in analogy to example 33 from 2-methoxymethyl-pyrrolidin.

Example 89

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 497.4 ($M+H^+$), was prepared in analogy to example 33 from piperidine.

Example 90

N-[1-Benzyl-2-(6-methoxy-1,3,4,9-tetrahydro-b-carbolin-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 575.5 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 8-methoxy-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole.

Example 91

N-(3,5-Difluoro-benzyl)-N'-[2-(4-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 561.5 ($M+H^+$), was prepared in analogy to example 33 from 4-hydroxy-1,2,3,4-tetrahydro-isoquinoline.

Example 92

N-[1-Benzyl-2-(6-fluoro-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 563.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 6-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole.

Example 93

N-(3,5-Difluoro-benzyl)-N'-[1-(ethyl-methyl-carbamoyl)-2-(1H-indol-3-yl)-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 471.3 ($M+H^+$), was prepared in analogy to example 33 from ethylmethylamine.

Example 94

N-(3,5-Difluoro-benzyl)-N'-[1-(1H-indol-3-ylmethyl)-2-(2-methyl-piperidin-1-yl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 511.5 ($M+H^+$), was prepared in analogy to example 33 from 2-methylpiperidine.

Example 95

N-(3,5-Difluoro-benzyl)-N'-(1-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-carbamoyl}-2-phenyl-ethyl)-2-methyl-malonamide

The title compound, MS: m/e = 568.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and N-methylhomoveratrylamine.

Example 96

N-[2-Azetidin-1-yl-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 469.3 ($M+H^+$), was prepared in analogy to example 33 from azetidine.

Example 97

N-(3,5-Difluoro-benzyl)-N'-[1-([1,3]dioxolan-2-ylmethyl-methyl-carbamoyl)-2-(1H-indol-3-yl)-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 529.4 ($M+H^+$), was prepared in analogy to example 33 from 2-methylaminomethyl-1,3-dioxolane.

Example 98

N-(3,5-Difluoro-benzyl)-N'-[2-(4-hydroxymethyl-piperidin-1-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide

The title compound, MS: m/e = 527.3 ($M+H^+$), was prepared in analogy to example 33 from 4-hydroxymethylpiperidine.

Example 99

N-[1-Benzyl-2-(8-fluoro-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl)-2-oxo-ethyl]-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 563.4 ($M+H^+$), was prepared in analogy to example 33 from L-phenylalanine-*tert*-butylester hydrochloride and 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole.

Example 100

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-propyl-malonamide

a) N-(3,5-difluoro-benzyl)-2-propyl-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl propyl-malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-propyl-malonamide, MS: m/e = 573.4 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-2-propyl-malonamic acid.

Example 101

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-isopropyl-malonamide

a) N-(3,5-Difluoro-benzyl)-2-isopropyl-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl isopropyl-malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-isopropyl-malonamide, MS: m/e = 573.3 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-2-isopropyl-malonamic acid.

Example 102

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-ethyl-malonamide

a) N-(3,5-Difluoro-benzyl)-2-ethyl-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl ethyl-malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-ethyl-malonamide, MS: m/e = 559.4 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-2-ethyl-malonamic acid.

Example 103

2-Allyl-N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-malonamide

a) N-(3,5-Difluoro-benzyl)-2-allyl-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl allyl-malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-allyl-malonamide, MS: m/e = 571.4 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-2-allyl-malonamic acid.

Example 104

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-fluoro-2-methyl-malonamide

a) N-(3,5-Difluoro-benzyl)-2-fluoro-2-methyl-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl 2-fluoro-2-methyl-malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-fluoro-2-methyl-malonamide, MS: m/e = 563.4 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-2-fluoro-2-methyl-malonamic acid.

Example 105

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-malonamide

a) N-(3,5-Difluoro-benzyl)-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-malonamide, MS: m/e = 531.3 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-malonamic acid.

Example 106

N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2,2-dimethyl-malonamide

a) N-(3,5-Difluoro-benzyl)-2,2-dimethyl-malonamic acid was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1) from diethyl 2,2-dimethyl-malonate.

b) N-(3,5-Difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2,2-dimethyl-malonamide, MS: m/e = 559.3 ($M+H^+$), was prepared in analogy to N-(3,5-difluoro-benzyl)-N'-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-2-methyl-malonamide (example 17) from N-(3,5-difluoro-benzyl)-2,2-dimethyl-malonamic acid.

Example 107

N-(7-Chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 525.1 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Example 108

N-(3,5-Difluoro-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-propyl-malonamide

The title compound, MS: m/e = 519.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and N-(3,5-difluoro-benzyl)-2-propyl-malonamic acid.

Example 109

2-*tert*-Butyl-N-(3,5-difluoro-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 533.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and N-(3,5-difluoro-benzyl)-2-*tert*-butyl-malonamic acid.

Example 110

N-(3,5-Difluoro-benzyl)-2-isopropyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 519.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and N-(3,5-difluoro-benzyl)-2-isopropyl-malonamic acid.

Example 111

N-(3,5-Difluoro-benzyl)-2-ethyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 505.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and N-(3,5-difluoro-benzyl)-2-ethyl-malonamic acid.

Example 112

N-(3,5-Difluoro-benzyl)-2-fluoro-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 495.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and N-(3,5-difluoro-benzyl)-2-fluoro-malonamic acid.

Example 113

N-(3,5-Difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 464.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one.

Example 114

N-(3,5-Difluoro-benzyl)-2-fluoro-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 482.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-fluoro-2-methyl-malonamic acid.

Example 115

N-(3,5-Difluoro-benzyl)-2-isopropyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 491.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-isopropyl-malonamic acid.

Example 116

N-(3,5-Difluoro-benzyl)-2-ethyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 478.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-ethyl-malonamic acid.

Example 117

N-(3,5-Difluoro-benzyl)-2-fluoro-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 468.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-fluoro-malonamic acid.

Example 118

N-(3,5-Difluoro-benzyl)-2,2-dimethyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 478.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H, 7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2,2-dimethyl-malonamic acid.

Example 119

N-(3,5-Difluoro-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-propyl-malonamide

The title compound, MS: m/e = 492.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-propyl-malonamic acid.

Example 120

2-Benzyl-N-(3,5-difluoro-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 539.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-benzyl-malonamic acid.

Example 121

2-*tert*-Butyl-N-(3,5-difluoro-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 506.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-*tert*-butyl-malonamic acid.

Example 122

N-(3,5-Difluoro-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 450.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-malonamic acid.

Example 123

Cyclopropane-1,1-dicarboxylic acid 3,5-difluoro-benzylamide (5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-amide

The title compound, MS: m/e = 476.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 1-(3,5-difluoro-benzylcarbamoyl)-cyclopropanecarboxylic acid.

Example 124

N-(4-Methoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) N-(4-Methoxy-benzyl)-2-methyl-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(4-Methoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 458.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(4-methoxy-benzyl)-2-methyl-malonamic acid.

Example 125

N-Benzyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) N-Benzyl-2-methyl-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-Benzyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 428.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-benzyl-2-methyl-malonamic acid.

Example 126

N-(3,4-Dimethoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) N-(3,4-Dimethoxy-benzyl)-2-methyl-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(3,4-Dimethoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 488.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,4-dimethoxy-benzyl)-2-methyl-malonamic acid.

Example 127

N-(4-Fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) N-(4-Fluoro-benzyl)-2-methyl-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(4-Fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 446.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(4-fluoro-benzyl)-2-methyl-malonamic acid.

Example 128

2-Methyl-N-(3-methyl-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(3-methyl-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) 2-Methyl-N-(3-methyl-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 442.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(3-methyl-benzyl)-malonamic acid.

Example 129

2-Methyl-N-(4-methyl-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(4-methyl-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) 2-Methyl-N-(4-methyl-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 441.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(4-methyl-benzyl)-malonamic acid.

Example 130

N-(4-Chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(4-chloro-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(4-Chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 462.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(4-chloro-benzyl)-malonamic acid.

Example 131

N-(3,5-Dichloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(3,5-dichloro-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(3,5-Dichloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 496.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(3,5-dichloro-benzyl)-malonamic acid.

Example 132

N-(3-Fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(3-fluoro-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(3-Fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 446.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(3-fluoro-benzyl)-malonamic acid.

Example 133

N-(3,5-Dimethoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(3,5-dimethoxy-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(3,5-Dimethoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 488.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(3,5-dimethoxy-benzyl)-malonamic acid.

Example 134

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3-trifluoromethyl-benzyl)-malonamide

a) 2-Methyl-N-(3-trifluoromethyl-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) 2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(3-trifluoromethyl-benzyl)-malonamide

The title compound, MS: m/e = 496.3 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(3-trifluoromethyl-benzyl)-malonamic acid.

Example 135

N-(2,5-Difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(2,5-difluoro-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) N-(2,5-Difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 464.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(2,5-difluoro-benzyl)-malonamic acid.

Example 136

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,3,5-trifluoro-benzyl)-malonamide

a) 2-Methyl-N-(2,3,5-trifluoro-benzyl)-malonamic acid

The title compound was prepared in analogy to N-(3,5-difluoro-benzyl)-2-methyl-malonamic acid (example 1).

b) 2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,3,5-trifluoro-benzyl)-malonamide

The title compound, MS: m/e = 482.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and 2-methyl-N-(2,3,5-trifluoro-benzyl)-malonamic acid.

Example 137

N-(4-Methoxy-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 485.4 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(4-methoxy-benzyl)-malonamic acid.

Example 138

N-Benzyl-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 455.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-benzyl-malonamic acid.

Example 139

N-(3,4-Dimethoxy-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 515.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(3,4-dimethoxy-benzyl)-malonamic acid.

Example 140

N-(4-Fluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 473.2 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(4-fluoro-benzyl)-malonamic acid.

Example 141

2-Methyl-N-(4-methyl-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 468.2 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(4-methyl-benzyl)-malonamic acid.

Example 142

2-Methyl-N-(3-methyl-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 468.2 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(3-methyl-benzyl)-malonamic acid.

Example 143

N-(4-Chloro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 489.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(4-chloro-benzyl)-malonamic acid.

Example 144

N-(3,5-Dichloro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 523.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(3,5-dichloro-benzyl)-malonamic acid.

Example 145

N-(3-Fluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 473.2 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(3-fluoro-benzyl)-malonamic acid.

Example 146

N-(3,5-Dimethoxy-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 515.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(3,5-dimethoxy-benzyl)-malonamic acid.

Example 147

2-Methyl-N-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-N'-(3-trifluoromethyl-benzyl)-malonamide

The title compound, MS: m/e = 523.4 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(3-trifluoromethyl-benzyl)-malonamic acid.

Example 148

N-(2,5-Difluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide

The title compound, MS: m/e = 491.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(2, 5-difluoro-benzyl)-malonamic acid.

Example 149

2-Methyl-N-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-N'-(2,3,5-trifluoro-benzyl)-malonamide

The title compound, MS: m/e = 509.3 ($M+H^+$), was prepared in analogy to example 17 from 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 2-methyl-N-(2,3,5-trifluoro-benzyl)-malonamic acid.

Example 150

N-{[(2-Benzyl-phenyl)-methyl-carbamoyl]-methyl}-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 480.3 ($M+H^+$), was prepared in analogy to example 17 from 2-amino-2'-benzyl-N-methylacetanilide.

Example 151

N-{[(4-Chloro-2-phenylsulfanyl-phenyl)-methyl-carbamoyl]-methyl}-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 533.4 ($M+H^+$), was prepared in analogy to example 17 from 2-amino-4'-chloro-N-methyl-2'-(phenylthio)acetanilide.

Example 152

N-{[(2-Benzoyl-4-chloro-phenyl)-methyl-carbamoyl]-methyl}-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide

The title compound, MS: m/e = 528.4 ($M+H^+$), was prepared in analogy to example 17 from 2-amino-2'-benzoyl-4'-chloro-N-methylacetanilide.

Example 153

N-(2-Fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

a) 2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid tert-butyl ester

To a cooled solution (0 °C) of 2-methyl-malonic acid mono-tert-butyl ester (1.01 g, 5.79 mmol) and 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one (1.15 g, 4.83 mmol) in THF (8 ml) was added hydroxybenzotriazole (652 mg, 4.83 mmol), diisopropylethylamine (624 mg, 4.83 mmol)and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (925 mg, 4.83 mmol), and the mixture was stirred overnight at r.t. The solvent was evaporated, the residue was taken up in ethyl acetate, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 395.3

(M+H+), (920mg, 48%) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH2Cl2).

b) 2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid

TFA (3ml) was added to a solution of 2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid tert-butyl ester (920 mg, 2.33 mmol) in dichloromethane (3 ml) and the mixture was stirred at r.t. overnight. The mixture was then taken up in more dichloromethane, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the title compound, MS: m/e = 339.3 (M+H+), (580 mg, 73 %) was obtained by chromatographic purification of the residue (silica gel, MeOH, CH_2Cl_2).

c) N-(2-Fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamic acid (20 mg, 0.059 mmol) and 2-fluorobenzylamine (7.4 mg, 0.059 mmol) were placed in a disposable polypropylene tube and dissolved in DMF (2 ml). TPTU (2-(2-pyridon-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, 19 mg, 0.065 mmol) was added, and the mixture was shaken overnight at r.t. The title compound, MS: m/e = 446.2 (M+H+), was isolated from the reaction mixture by automated, preparative HPLC (YMC CombiPrep C18 column 50 x 20mm, solvent gradient 5 - 95 % CH_3CN in 0.1 % TFA(aq) over 6.0 min, λ = 230 nm, flow rate 40 ml/min).

Example 154

N-(2-Chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 462.2 (M+H+), was prepared in analogy to example 153 from 2-chlorobenzylamine.

Example 155

2-Methyl-N-(2-methyl-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 442.3 (M+H+), was prepared in analogy to example 153 from 2-methylbenzylamine.

Example 156

N-(2-Methoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 458.3 (M+H+), was prepared in analogy to example 153 from 2-methoxybenzylamine.

Example 157

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2-trifluoromethyl-benzyl)-malonamide

The title compound, MS: m/e = 496.3 (M+H+), was prepared in analogy to example 153 from 2-trifluoromethylbenzylamine.

Example 158

N-(3-Methoxy-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 458.3 (M+H+), was prepared in analogy to example 153 from 3-methoxybenzylamine.

Example 159

N-(3-Chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 462.2 (M+H+), was prepared in analogy to example 153 from 3-chlorobenzylamine.

Example 160

2-Methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(4-trifluoromethyl-benzyl)-malonamide

The title compound, MS: m/e = 496.3 ($M+H^+$), was prepared in analogy to example 153 from 4-trifluorobenzylamine.

Example 161

N-(3,5-Difluoro-benzyl)-2-methoxy-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide

The title compound, MS: m/e = 480.2 ($M+H^+$), was prepared in analogy to example 17 from 7-amino-5-methyl-5H,7H-dibenzo[b,d]azepin-6-one and N-(3,5-difluoro-benzyl)-2-methoxy-malonamic acid.

Example 162

(2S-cis)-N-(2-Carbamoyl-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-N'-(3,5-difluoro-benzyl)-(2R,S)-methyl-malonamide

Solid phase synthesis was performed on a benzhydrylamine polystyrene resin, functionalized with an Fmoc-amide linker, p-[(R,S)-a-1-(9H-fluoren-9-yl)methoxyformamido-2,4-dimethoxybenzyl]phenoxyacetic acid.

The functionalized resin (300 mg., 0.6 mmol/g loading) was treated with 20 % piperidine/DMF (10 ml, 10 min) and then washed (3 x alternating DMF/isopropanol). (2S-cis)-5-(9H-fluoren-9-yl)methoxycarbonylamino-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indole-2-carboxylic (127 mg, 0.27 mmol), O-(1,2-dihydro-2-oxopyridyl-1-yl)-N,N,N',N'-tetramethyluroniumtetrafluoroborate (TPTU) (80 mg, 0.41 mmol), diisopropylethylamine (140 µl, 1.22 mmol) and DMF (5 ml) were added to the resin. The mixture was shaken for 1 h. (Ninhydrin test: negative) and the resin was filtered and washed as above. (131 mg, 0.54 mmol), TPTU (160 mg, 0.54 mmol), diisopropylethylamine (280 µl, 1.62 mmol) and DMF (5 ml) were added to the resin and coupled as above. Product was cleaved from the resin using 90 %TFA aqueous (5 ml) for 1 h. The filtrate was concentrated under reduced pressure and purified by prep. RP(C18)HPLC. Desired fractions were pooled and lyophilized: 30 mg, MS: 471.2 (MH^+ (60 %)), 493.1 (MNa^+ (100), 426.3 (MH^+-$CONH_2$) ;

Example 163

(2S-cis)-N-(2-Cyano-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-N'-(3,5-difluoro-benzyl)-(2R,S)-methyl-malonamide

A mixture containing (2S-cis)-N-(2-carbamoyl-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-N'-(3,5-difluoro-benzyl)-(2R,S)-methyl-malonamide (18.5 mg, 0.04 mmol) , methoxycarbonylsulfamoyl-triethylammonium hydroxide (Burgess reagent) (19 mg, 0.08 mmol) in THF (1.5 ml) was shaken for 30 h at 70 °C under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and ethyl acetate was added. The organic phase was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by prep.RP(C18)HPLC: 10 mg, MS: 530.1 (MH+(100 %)), 552.1 (MNa+(30));

Example 164

(2S-cis)-N-(3,5-Difluoro-benzyl)-2-methyl-N'-{4-oxo-2-[(2-thiophen-2-yl-acetylamino)-(2R,S)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-malonamide

a) (2S-cis)-(2-Cyano-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-carbamic acid tert-butyl ester

9-Fmoc-aminoxanthen-3-yloxy-methyl resin (Sieber Amide resin; Calbiochem-Novabiochem AG) (5 g, 0.52 mmol/g loading) was treated with 20 % piperidine/DMF (50 ml, 10 min) and then washed (3 x alternating DMF/isopropanol). (2S-cis)-5-(9H-Fluoren-9-yl)methoxycarbonylamino-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indole-2-carboxylic (1.83 g, 3.9 mmol), TPTU (1.2 g, 3.9 mmol), diisopropylethylamine (3 ml, 17.6 mmol) and DMF (10 ml) were added to the resin. Coupling was allowed to proceed for 1 h (Ninhydrin test: negative) and the resin was filtered and washed as before. Fmoc group removal was followed by t-Boc group amine protection using t-Boc anhydride (5.7 g, 26 mmol) diisopropylethylamine (2.2. ml, 13 mmol) in 12 ml dichloromethane. The washed, dried resin was treated with trifluoroacetic anhydride (1.8 ml, 13 mmol), pyridine (2.1 ml, 26 mmol) in 15 ml dichloromethane for 16 h at room temperature. The filtrate was collected and the resin washed (CH_2Cl_2, 2x10 ml). The combined organic fractions were washed with 5 % $NaHCO_3$, dried ($MgSO_4$) filtered and concentrated under reduced pressure yielding a crude oil which was purified by flash chromatography (ethyl acetate-n-hexanes 1:3): 0.71 g; MS: 328.3 (MH^+(20 %)); 228.2 (MH^+-Boc(100)).

b) (2S-cis)-{4-Oxo-2-[(2-thiophen-2-yl-acetylamino)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-carbamic acid tert-butyl ester

(2S-cis)-(2-Cyano-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-carbamic acid tert-butyl ester (0.59 g, 1.80 mmol) was hydrogenated over palladium on carbon (10 %, 0.22 g) in 80 ml acetic acid for 1 h. The mixture was filtered (Decalite) and the filtrate was lyophilized: 0.33 g white solid. A part of this lyophilisate (0.16 g, 0.48 mmol) was dissolved in 8 ml DMF and was coupled to thiophene-2-acetic acid (0.21 g, 1.45 mmol) in the presence of TPTU (0.43 g, 1.45 mmol), diisopropylethylamine (0.84 ml, 5 mmol) for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and washed successively with 1N $NaHCO_3$, 0.2 N $KHSO_4$, water and the organic phase was dried ($MgSO_4$) filtered and concentrated under reduced pressure, Purification by flash chromatgraphy (ethyl acetate.n.hexanes 3:1): white foam, 125 mg; MS: 456.3 (MH^+(60 %)).

c) (2S-cis)-N-(3,5-Difluoro-benzyl)-2-methyl-N'-{4-oxo-2-[(2-thiophen-2-yl-acetylamino)-(2R,S)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-malonamide

(2S-cis)-{4-Oxo-2-[(2-thiophen-2-yl-acetylamino)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-carbamic acid tert-butyl ester was treated with 4 M HCl/ 1,4-dioxan (3 ml) for 1 h at room temperature and the reaction mixture was concentrated under reduced pressure and concentrated another two times from acetonitrile. The hydrochloride salt (ca. 20 mg) was dissolved in 1 ml DMF and the pH of the solution was adjusted to 8. Malonic acid derivative, (41 mg, 0.17 mmol) TPTU (50 mg, 0.17 mmol) diisopropylethylamine (87 µl , 0.51 mmol) in 0,5 ml DMF were added and the reaction mixture was shaken for 1 h. The reaction mixture was acidified with acetic acid, concentrated to a smaller volume and directly purified by prep.RP(C18)HPLC: 14.5 mg, MS: 581.1 (MH^+(100 %));

Example 165

(2S-cis)-N-(3,5-Difluoro-benzyl)-N'-(2-{[2-(4-fluoro-phenyl)-acetylamino]-methyl}-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-(2R,S)-methyl-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 164 using 4-fluorophenylacetic acid instead of thiophene-2-acetic acid: 15.8 mg, MS: 593.2 (MH^+(100 %));

Example 166

(2S-cis)-N-(3,5-Difluoro-benzyl)-2,2-dimethyl-N'-{4-oxo-2-[(2-thiophen-2-yl-acetylamino)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-malonamide

The title compound was obtained in comparable yields according to the procedures described for example 164 using malonic acid derivative N-(3,5-difluorobenzyl)-2,2-dimethyl-malonamic acid instead of derivative N-(3,5-difluorobenzyl)-2-methyl-malonamic acid: 15.0 mg, MS: 595.1 (MH^+(100 %));

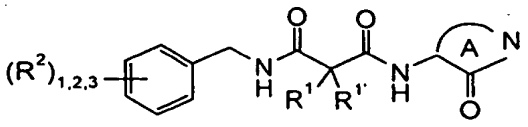
Example 167

(2S-cis)-N-(3,5-Difluoro-benzyl)-N'-(2-{[2-(4-fluoro-phenyl)-acetylamino]-methyl}-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-2,2-dimethyl-malonamide

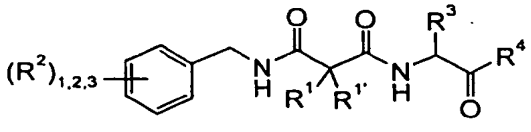
The title compound was obtained in comparable yields according to the procedures described for example 164 using 4-fluorophenylacetic acid instead of thiophene-2-acetic acid and malonic acid derivative N-(3,5-difluorobenzyl)-2,2-dimethyl-malonamic acid instead of N-(3,5-difluorobenzyl)-2-methyl-malonamic acid: 5.4 mg, MS: 607.1 (MH^+(100 %));

Claims

1. Compounds of the general formula



IA or



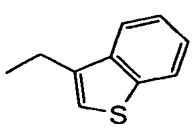
IB

wherein

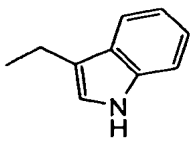
R^1 and $R^{1'}$ are the same or different and are hydrogen, lower alkyl, halogen, benzyl, lower alkenyl or are together with the carbon atom to which they are attached lower cycloalkyl;

$(R^2)_{1,2,3}$ is independently from each other hydrogen, halogen, lower alkyl, lower alkoxy or trifluoromethyl;

R^3 is phenyl or benzyl, which are unsubstituted or substituted by one or two substituents, selected from the group consisting of halogen or cyano, or is
- lower alkyl,
- two hydrogen atoms,
- $-(CH_2)_{1,2}$-S-lower alkyl,
- $(CH_2)_{1,2}$-cycloalkyl,
- $(CH_2)_{1,2}$-OH,
- CH_2OCH_2-phenyl, or the groups



or

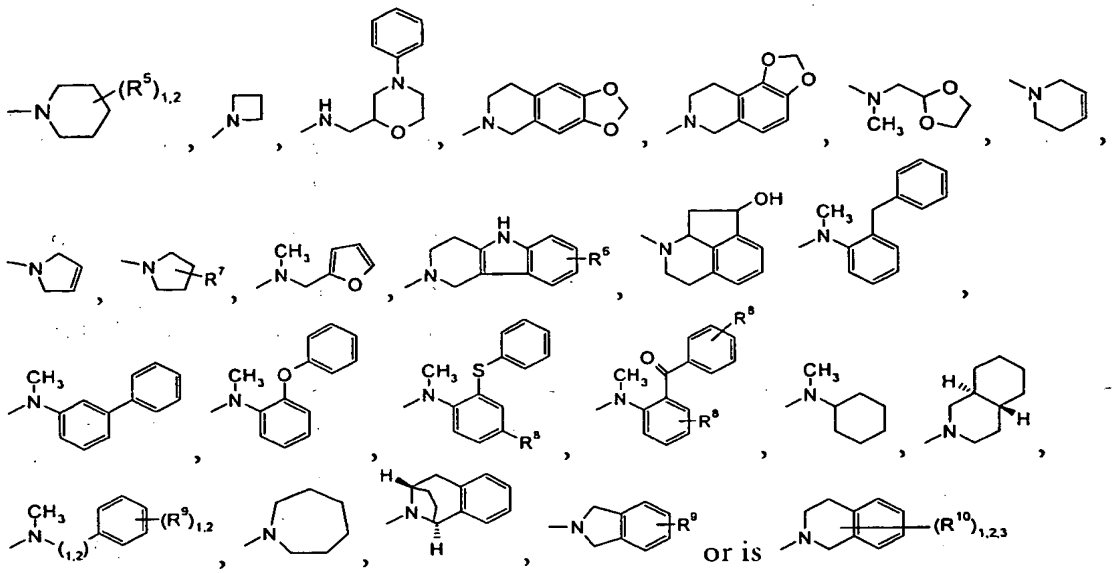


;

R^4 is lower alkoxy,
- mono-or dialkyl amino,
- $N(CH_3)(CH_2)_{1,2}$-C≡CH,

or is a mono-, di or tricyclic group, unsubstituted or substituted by R^5 to R^{10}, and

which groups may be linked by $-N(CH_3)(CH_2)_{0,1,2,}$ to the –C(O) –group in formula IB, selected from the group consisting of



wherein

$(R^5)_{1,2}$ is independently from each other hydrogen, halogen, lower alkyl or $-(CH_2)_{1,2}OH$;

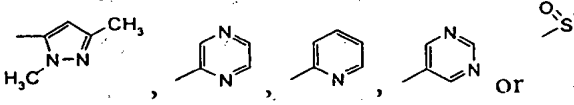
R^6 is hydrogen, halogen or lower alkoxy;

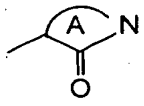
R^7 is hydrogen or $-CH_2OCH_3$;

R^8 is hydrogen or halogen;

R^9 is hydrogen, lower alkoxy, lower alkyl or amino;

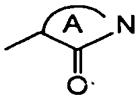
$(R^{10})_{1,2,3}$ is independently from each other hydrogen, lower alkyl, lower alkoxy, lower cycloalkyl, halogen, hydroxy, =O, amino, nitro, $-CH_2CN$, $-OCH_2C_6H_5$,

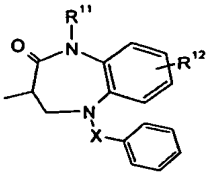
or the groups  ;



may be one of the following rings

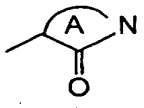
N-(3,5-difluoro-benzyl)-2-fluoro-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide,
N-(3,5-difluoro-benzyl)-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-propyl-malonamide,
N-(3,5-difluoro-benzyl)-2-ethyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide or
N-(4-chloro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide.

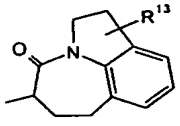
7. Compounds of formula IA in accordance with claim 1, wherein  is



8. Compounds of formula IA in accordance with claim 7, which compounds are

N-(5-benzyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide,
N-(5-benzenesulfonyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide or
N-(5-benzoyl-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-N'-(3,5-difluoro-benzyl)-2-methyl-malonamide.

9. Compounds of formula IA in accordance with claim 1, wherein  is



10. Compounds of formula IA in accordance with claim 9, wherein the compounds are

(2S-cis)-N-(3,5-difluoro-benzyl)-2-methyl-N'-{4-oxo-2-[(2-thiophen-2-yl-acetylamino)-(2R,S)-methyl]-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl}-malonamide or

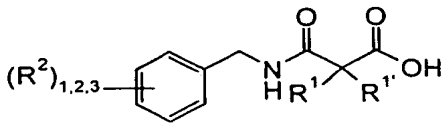
(2S-cis)-N-(3,5-difluoro-benzyl)-N'-(2-{[2-(4-fluoro-phenyl)-acetylamino]-methyl}-4-oxo-1,2,4,5,6,7-hexahydro-azepino[3,2,1-hi]indol-5-yl)-2,2-dimethyl-malonamide.

11. Compounds of formula IB in accordance with claim 1.

12. Compounds of formulas IA or IB in accordance with claim 1, wherein at least one of $(R^2)_{1,2,3}$ is fluoro.

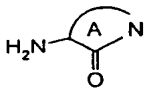
13. A process for preparing a compound of formula IA or IB as defined in claims 1 – 12, which process comprises

a) reacting a compound of formula



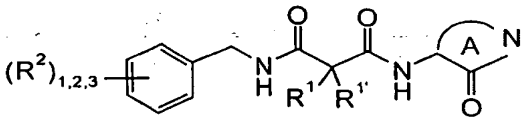
VI

with a compound of formula



VII

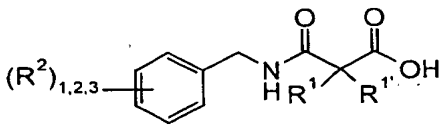
to a compound of formula



IA

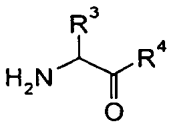
or

b) reacting a compound of formula



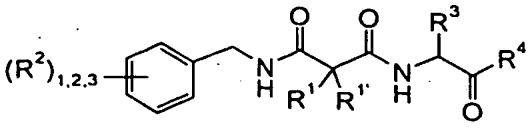
VI

with a compound of formula



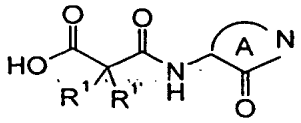
VIII

to a compound of formula



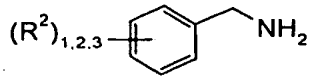
IB

c) reacting a compound of formula



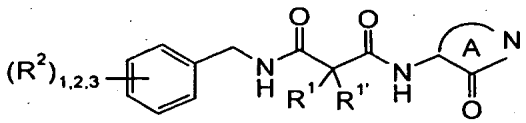
X

with a compound of formula

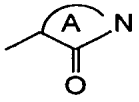


IV

to a compound of formula



IA

wherein the substituents R^1, $R^{1'}$, R^2 and the group  are described above, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

14. A compound according to any on of claims 1 – 12, whenever prepared by a process as claimed in claim 13 or by an equivalent method.

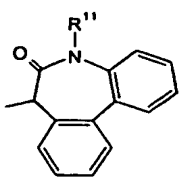
15. A medicament containing one or more compounds as claimed in any one of claims 1 – 12 and pharmaceutically acceptable excipients.

16. A medicament according to claim 15 for the treatment of Alzheimer's disease.

17. The use of a compound in any one of claims 1 – 12 for the manufacture of medicaments for the teratment of Alzheimer's disease.

18. The invention as hereinbefore described.

5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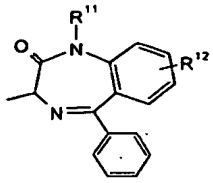
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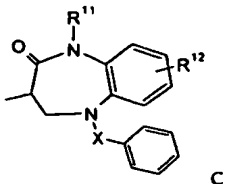
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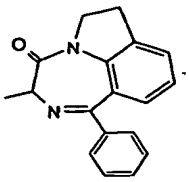
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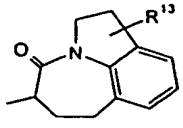
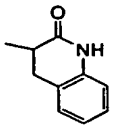
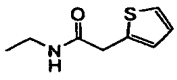
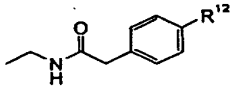

e) or

f);

wherein

X is $-CH_2$, $-S(O)_2$ or $-C(O)-$;

R^{11} is hydrogen or lower alkyl;

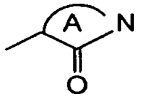
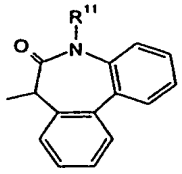
R^{12} is hydrogen or halogen;

R^{13} is hydrogen, CN, hydroxy, $-C(O)NH_2$, or  or  ;

and pharmaceutically suitable acid addition salts thereof.

2. Compounds of formula IA in accordance with claim 1.

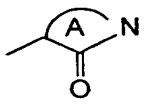
3. Compounds of formula IA in accordance with claims 1, wherein

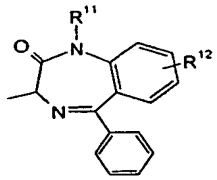

is

.

4. Compounds of formula IA in accordance with claim 3, which compounds are

N-(3,5-difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(3,5-difluoro-benzyl)-2-fluoro-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(3,5-difluoro-benzyl)-2-isopropyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(3,5-difluoro-benzyl)-2-ethyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,

N-(3,5-difluoro-benzyl)-2-fluoro-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(3,5-difluoro-benzyl)-2,2-dimethyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(3,5-difluoro-benzyl)-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-2-propyl-malonamide,
N-benzyl-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(4-fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(4-chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(3-fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(2,5-difluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
2-methyl-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-N'-(2,3,5-trifluoro-benzyl)-malonamide,
N-(2-fluoro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide,
N-(2-chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide or
N-(3-chloro-benzyl)-2-methyl-N'-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)-malonamide.

5. Compounds of formula IA in accordance with claims 1, wherein  is



6. Compounds of formula IA in accordance with claim 5, wherein the compounds are
(N-(3,5-difluoro-benzyl)-2-methyl-N'-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-malonamide,